Penalized Competing Risks Analysis using Case-base sampling

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Overview

1. Background and Motivation

2. Proposed Method

3. Simulation Study

1. Variable Selection
2. CIF Prediction

4. Discussion and Future Work

Background

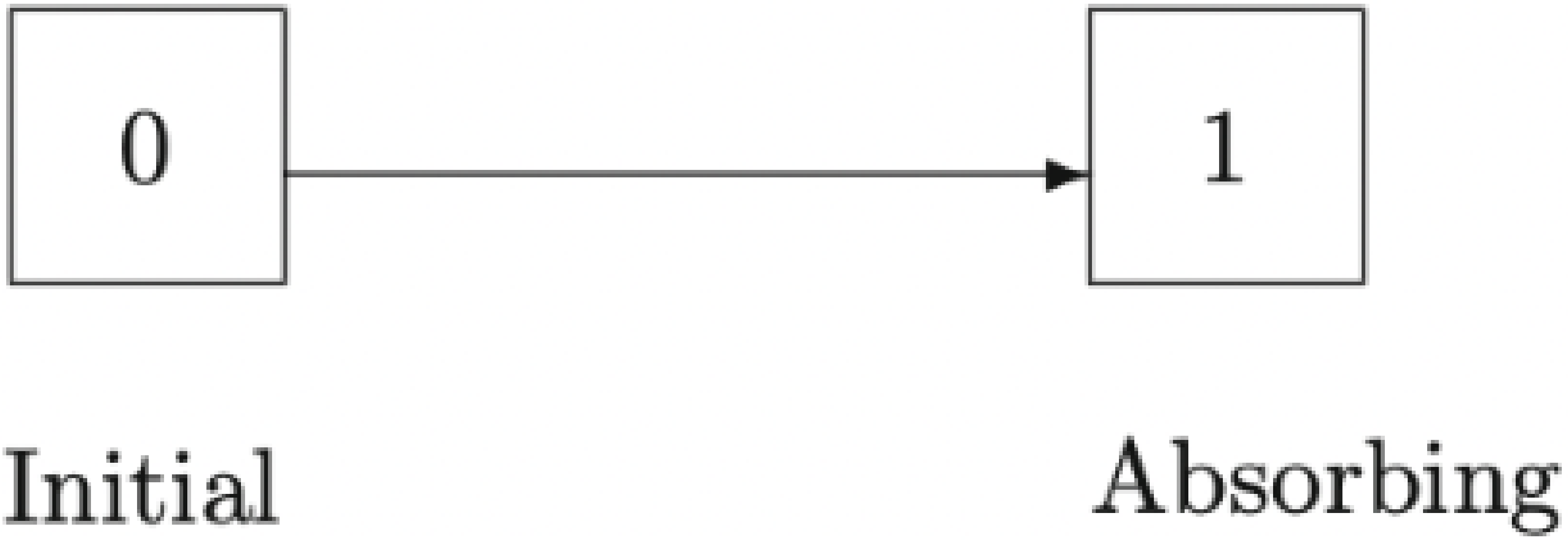
Survival Analysis

- Quantify expected time to event, e.g. death, onset of disease

Proportion of a population which will survive past a certain time?

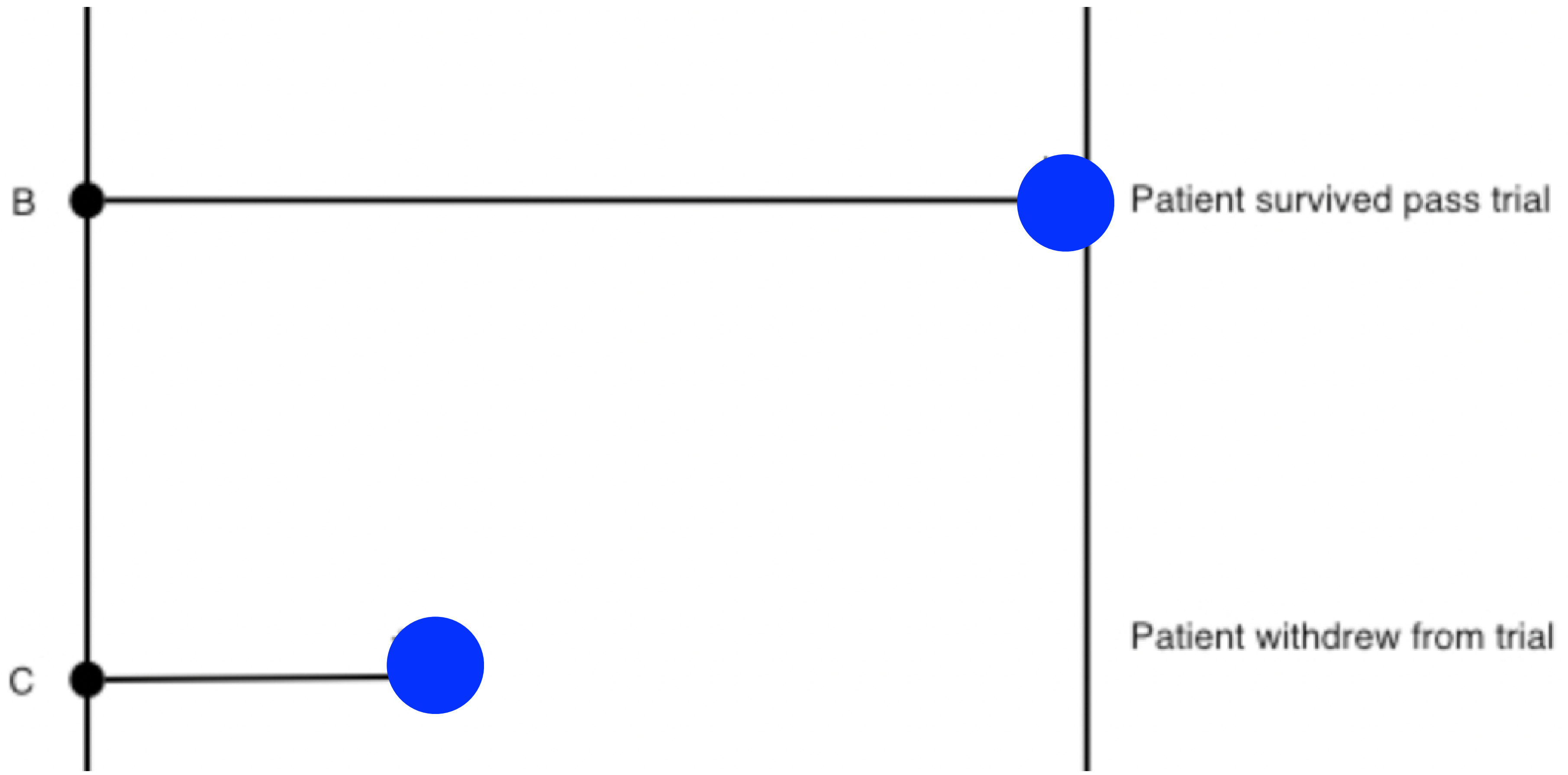
Of the surviving population, at what rate will they eventually experience the event?

How do particular characteristics affect event rate?



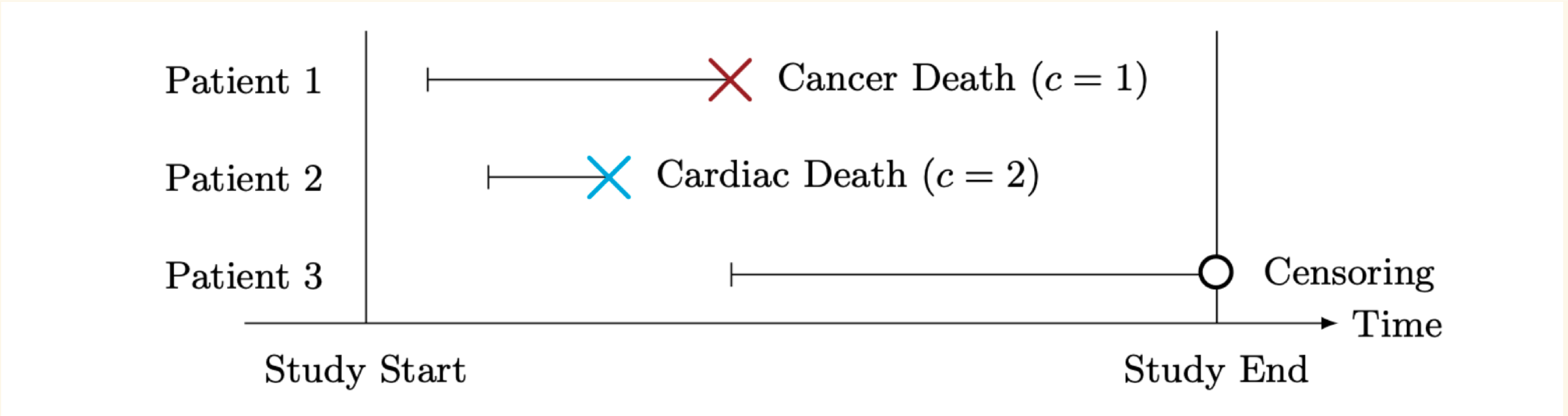
Censoring is common issue in survival analysis

- **Follow individuals typically for a fixed study period**
- When study ends, some individuals still have not experienced event yet
- Individuals drop out: event status unknown



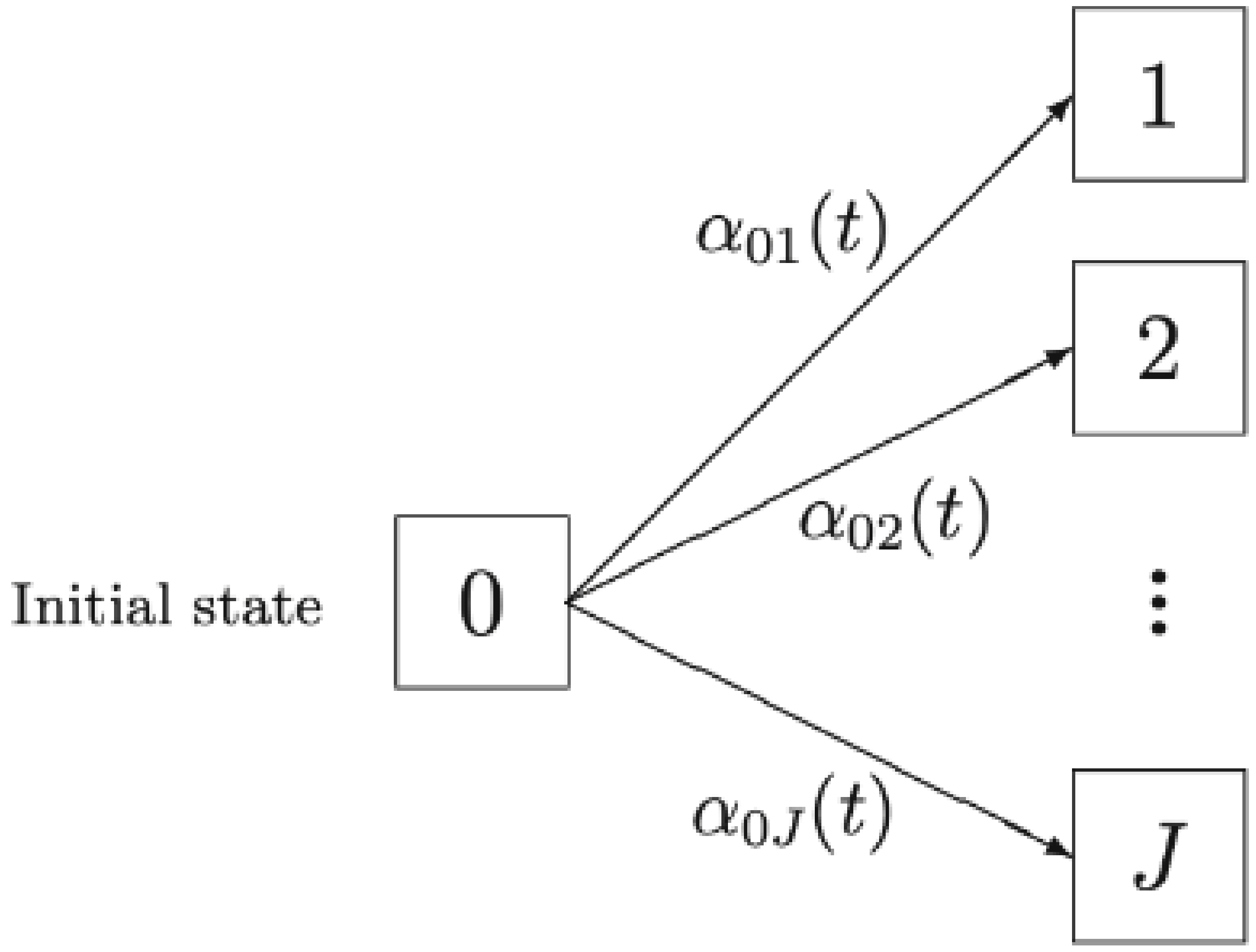
Competing Risks: Extension of Survival Analysis

- In real life, subjects can potentially experience more than one type of a certain event



Competing Risks: Extension of Survival Analysis

- Naive survival analysis: treat other event as censored
- Individual is no longer *at risk* of experiencing event of interest



Outcomes of Interest in Survival Analysis

1. Hazard

2. Cumulative incidence

Survival Analysis: Hazard

- **Describes rate:** instantaneous risk of event *J* for subjects that are currently **event-free**
- **Quantify risk factors:** *"1-unit change in Age can increase the rate of occurrence of event by 2.11"*

$$\alpha(t) \cdot dt := \lim_{\Delta t \searrow 0} \frac{P(T \in [t, t + \Delta t) | T \geq t)}{\Delta t}$$

Survival Analysis: Cumulative Incidence (CIF)

- **Describes risk:** Probability of occurrence of event of interest/*incidence* over time
- *"5-year risk of event for Patient X is 0.57"*

$$P(T \leq t) = \int_0^t P(T > u-)\alpha(u)du$$

Motivation

What should we model in a survival analysis?

Interested in risk factors?

Model cause-specific hazard

- Quantify effects of covariates on the rate of the outcome in subjects

Interested in predicting patient outcome?

Model cause-specific cumulative incidence

- Estimate patient prognosis
- Inform clinical patient management

Competing Risks Models: Cox Proportional Hazards

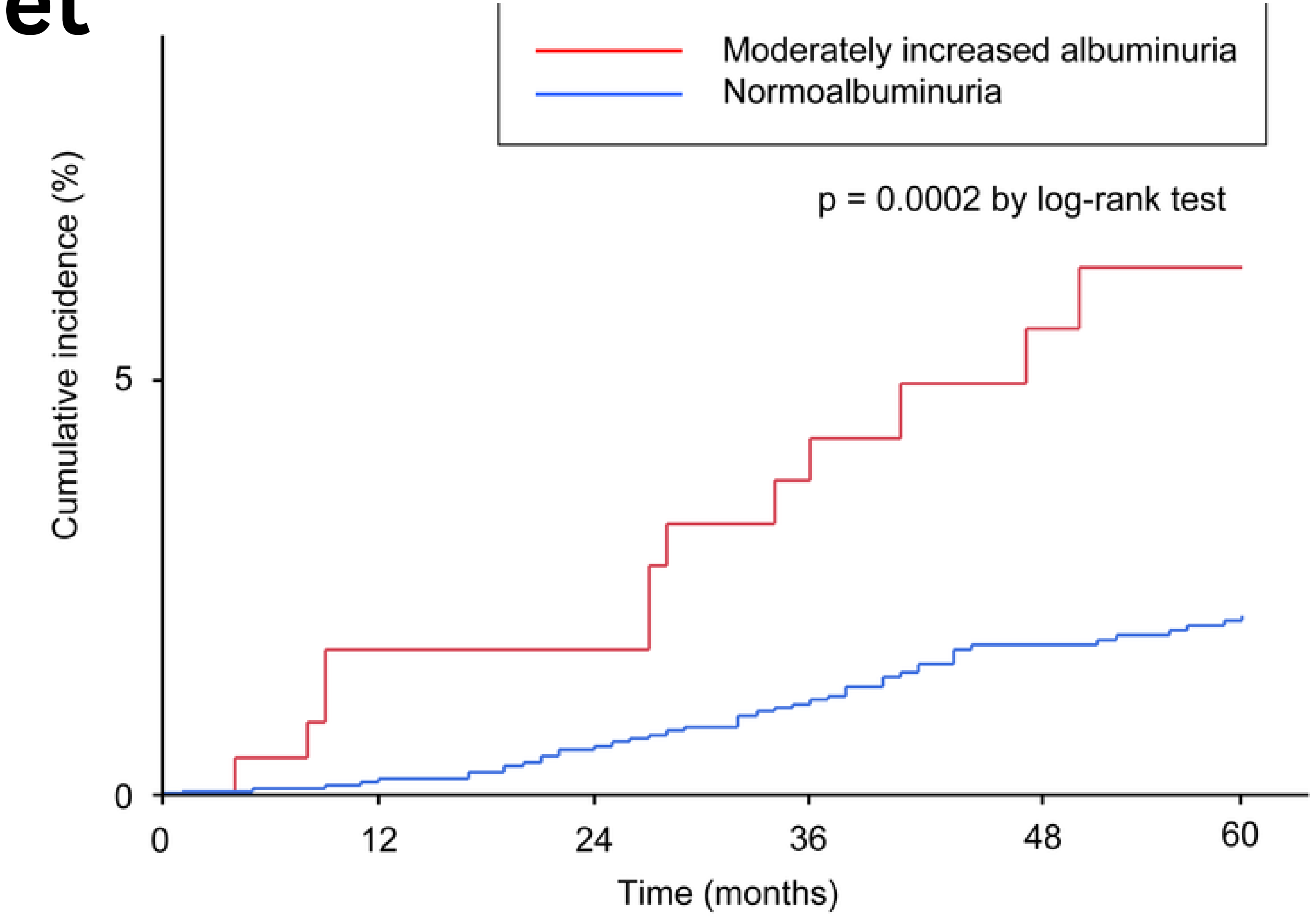
$$h(t|x_i) = h_0(t)\exp(\mathbf{x}_i^T\boldsymbol{\beta})$$

- Models **cause-specific hazards:** subjects who are event free
- **Flexible semi-parametric approach:** measures relative risk through hazards ratio
- **Proportional Hazards Assumption:** Baseline hazard not explicitly modelled

$$\frac{h(t|X_1)}{h(t|X_2)} = \frac{h_0(t)\cdot\exp(\beta_1 X_1)}{h_0(t)\cdot\exp(\beta_2 X_2)} = \frac{\exp(\beta_1 X_1)}{\exp(\beta_2 X_2)}$$

Competing Risks Models: Cox Proportional Hazards

- Treats competing risk as censored
- **To estimate CIF:** Have to estimate baseline hazard separately
- Produces **non-parametric,** step-wise estimates of cumulative incidence: **difficult to interpret**



Number at risk

Moderately increased albuminuria	237	226	209	189	143	128
Normoalbuminuria	2824	2704	2516	2154	1779	1618

Competing Risks Models: CIF Models

- E.g. Fine Gray model
- **Model CIF through sub-distribution hazards:** Consider **event-free** and individuals who have **experienced competing event**
- **One-to-one relationship with CIF**
- Produces **non-parametric** CIF estimates that account for competing risks
- Also produces step-wise estimates of CIF

Overview of competing risks models

Cause-Specific Hazards Models

☑ Quantify Risk Factors: easy to interpret

☑ Treat competing risks as censored

CIF Models

☑ Quantify clinical prognosis

☑ Account for competing risks

☑ Produce step-wise estimates of CIF (difficult to interpret)

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Proposed Method

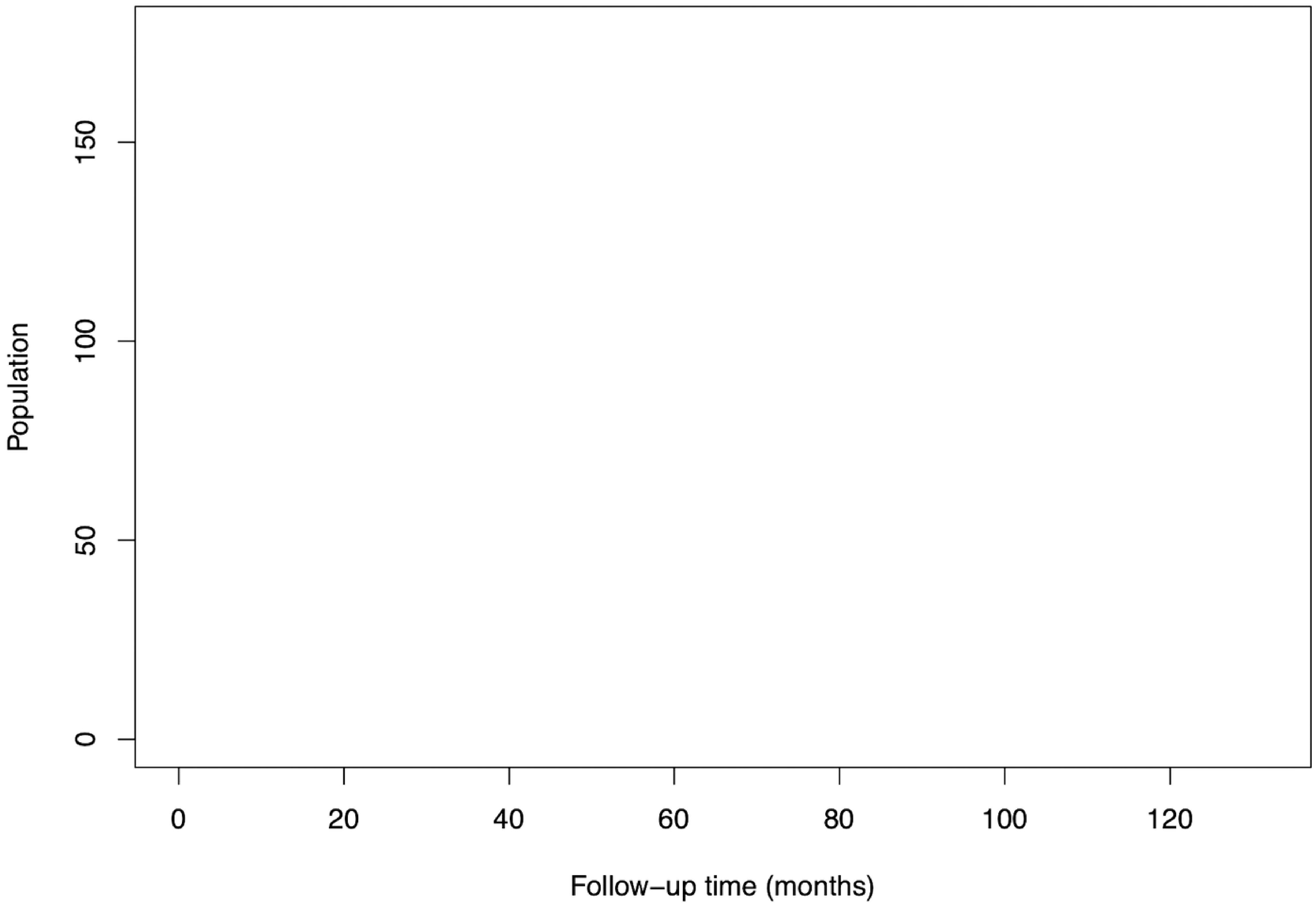
Solution: Casebase framework (Bhatnagar et al., 2020)

- Models the cause-specific hazard directly using (smooth) parametric distribution families

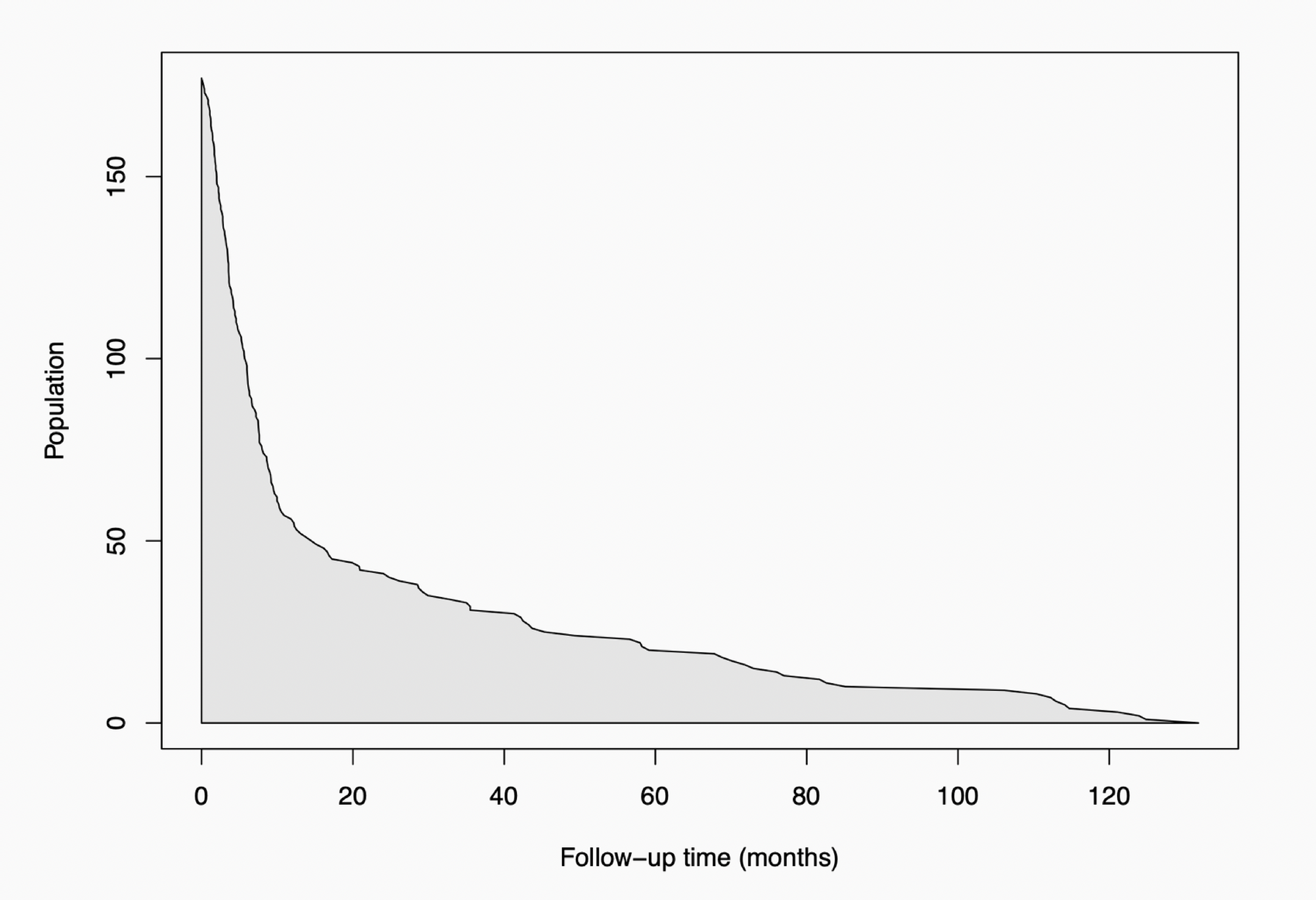
- Produces smooth CIF curves, adjusting for competing risks

- Based on Hanley & Miettinen’s (2009) case base sampling method

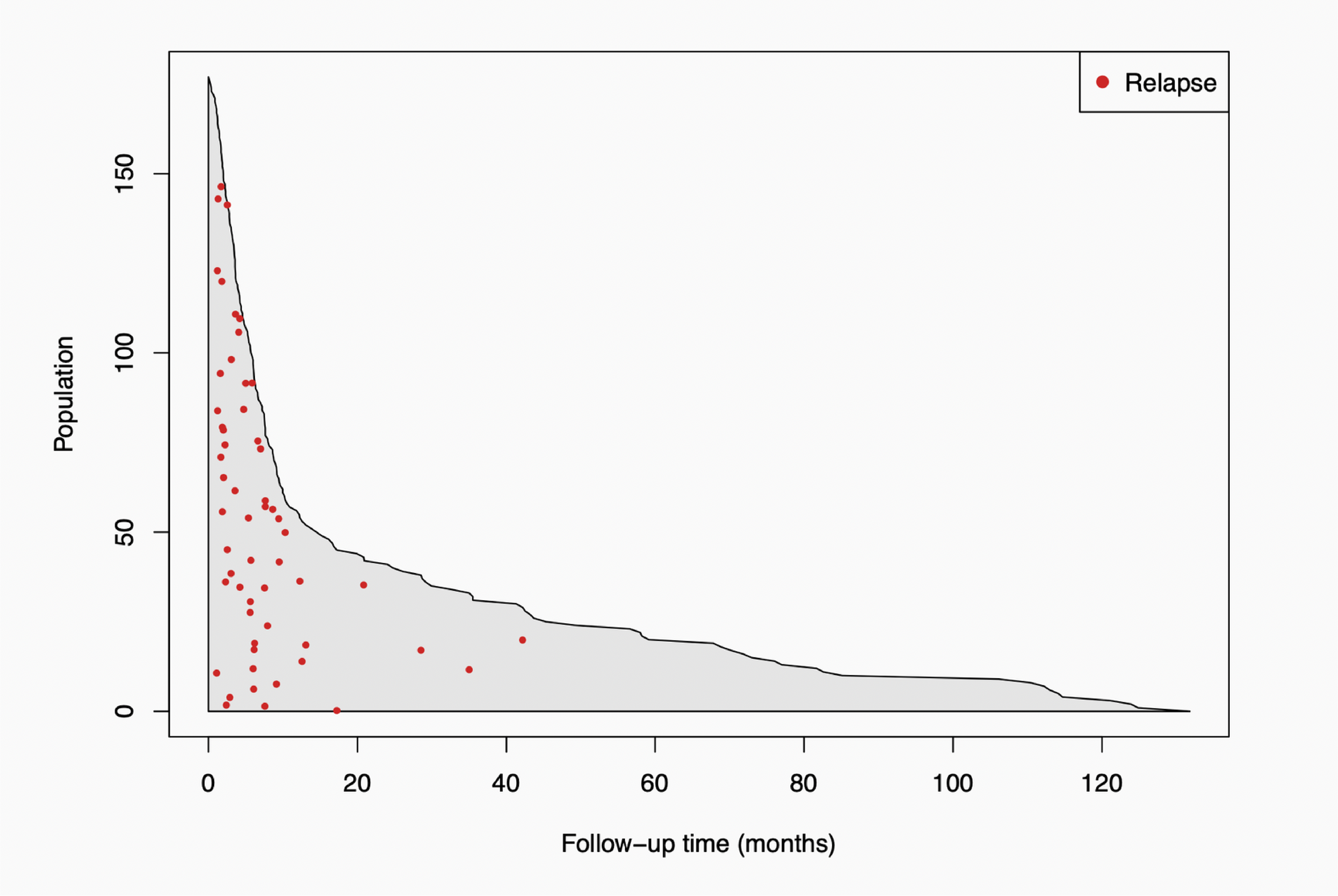
Casebase sampling



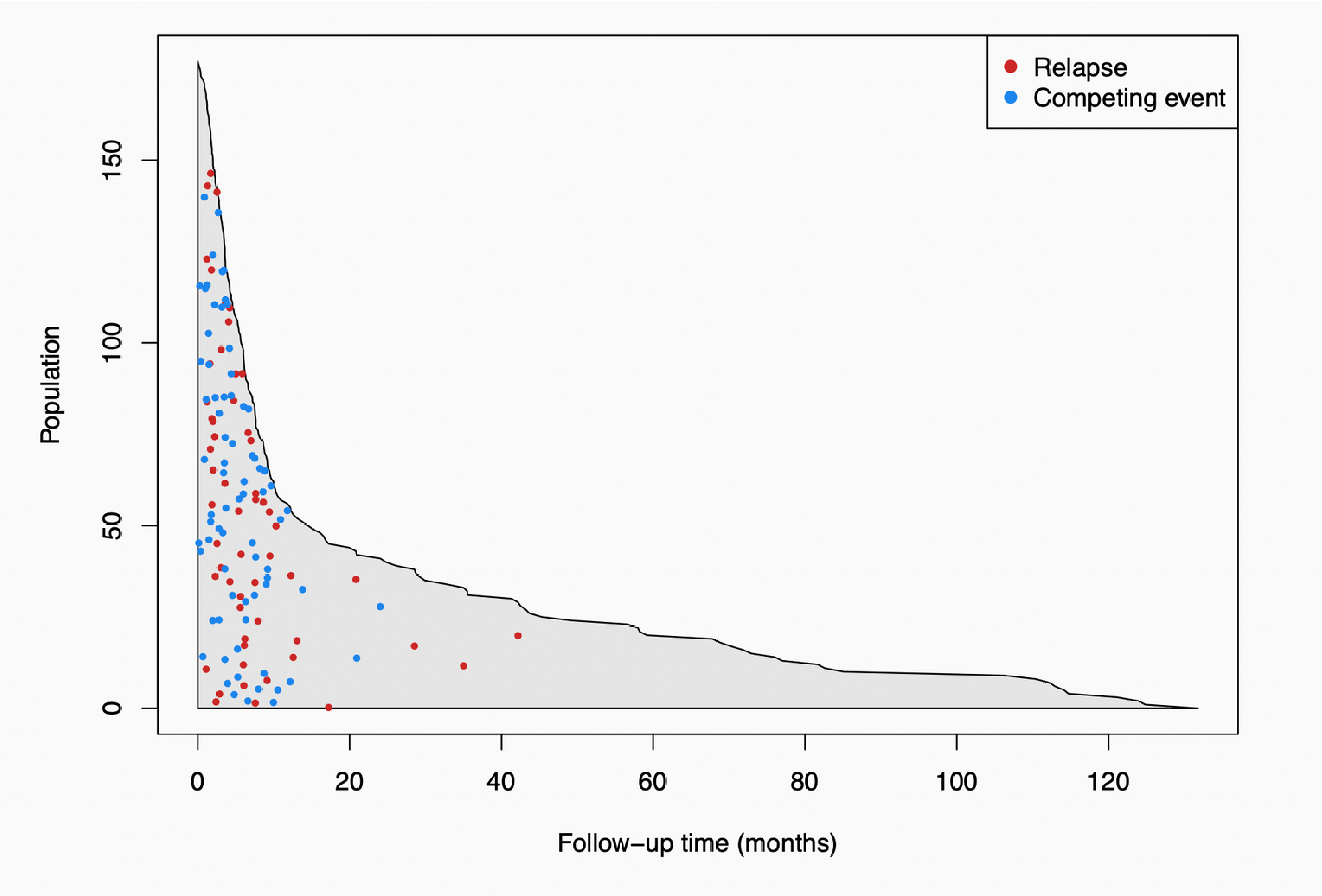
Casebase sampling



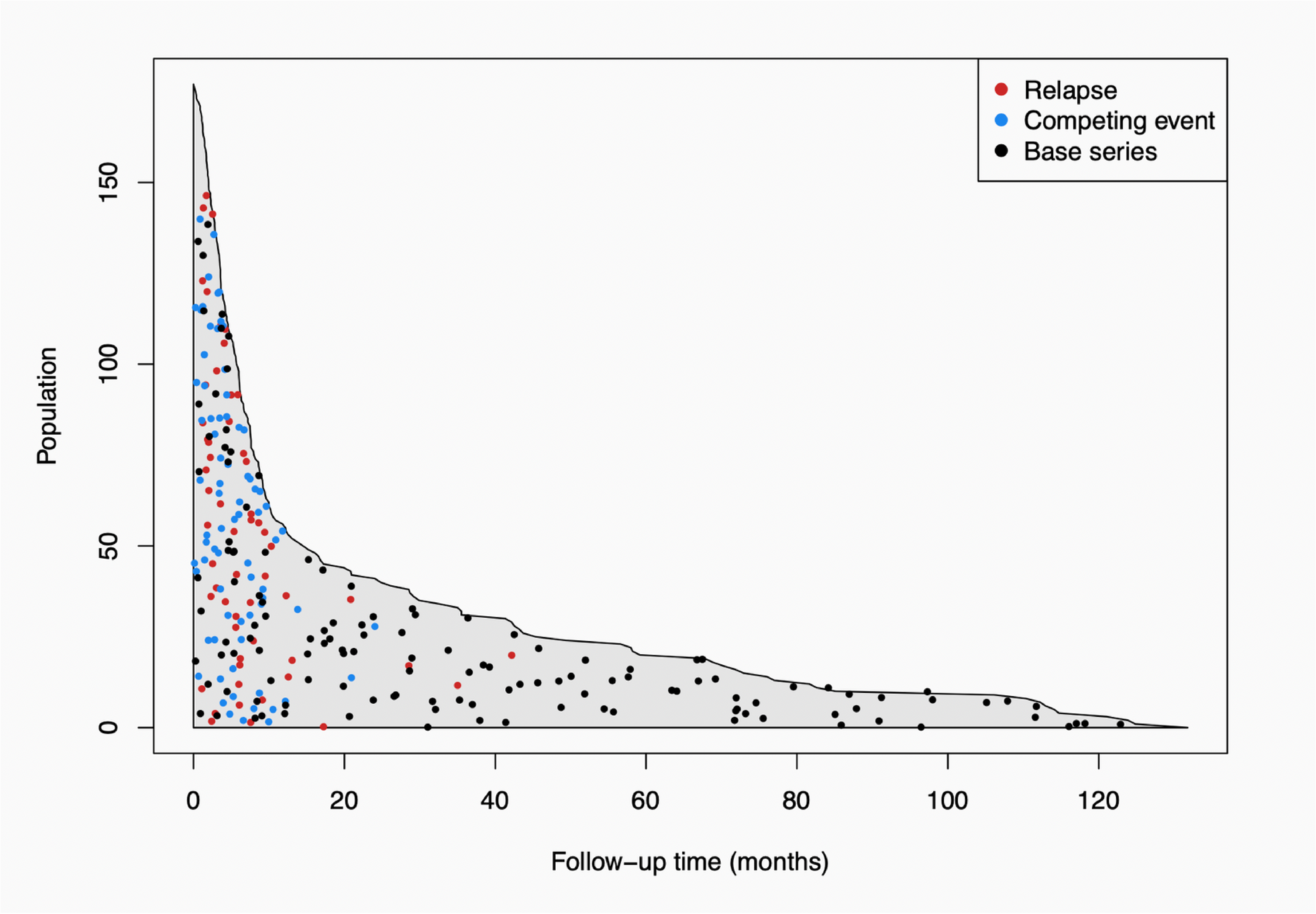
Casebase sampling



Casebase sampling



Casebase sampling



Casebase framework

Let $N_i(t) \in \{0, 1, 2\}$ be counting processes corresponding to the event for individuals $i = 1, \ldots n$

We model the hazard function to satisfy:

$$\lambda_i(t)dt = E[dN_i(t) \mid \text{past}].$$

Casebase framework

We model the hazard function to satisfy:

$$\lambda_i(t)dt = E[dN_i(t) \mid \text{past}]$$

If the hazard function $\lambda_i(t;\theta)$ is parameterized in terms of θ we can define an estimator by maximizing the likelihood:

$$L_0(\theta) = \prod_{i=1}^{n} \exp\left\{-\int_0^{\min(t_i,\tau)} \lambda_i(t;\theta)dt\right\} \prod_{i=1}^{n} \prod_{t\in[0,\tau)} \lambda_i(t;\theta)^{dN_i(t)},$$

Casebase framework

- By conditioning on person-moments through case-base sampling, we can avoid computing the integral

We can define an estimating equation for θ as follows:

$$L(\theta) = \prod_{i=1}^{n} \prod_{t \in [0,\tau]} \left(\frac{\lambda_j(t)^{dN_j(t)}}{\rho_i(t) + \sum_{j=1}^{J} \lambda_j(t)} \right)$$

where $$\rho_i(t) = \frac{\text{N in base series}}{\text{Total population time of study-base}}$$

- Corresponds to multinomial likelihood with offset $\log(1/\rho_i(t))$.

Casebase Estimation: Multinomial Regression

- Multinomial Regression parameterization:

$$\log \frac{\Pr(G=l|x,t)}{\Pr(G=K|x,t)} = \beta_{0l} + x^T\beta_l + \log(B/b), \quad l = 1, \ldots\ldots, K-1$$

- **glmnet** uses symmetric parameterization: does not estimate offset
- Optimize using stochastic variance reduced gradient (SVRG) (Johnson and Zhang., 2013): fast convergence for *p* > *n*
- Implemented in **mtool** package

$$\min_{\theta \in \mathbb{R}^p} -\ell(\theta) + \sum_{i=1}^{p} w_j \lambda \left(\frac{1-\alpha}{2} \sum_{k=1}^{p} |\theta_{j_k}| + \frac{\alpha}{2} \sum_{k=1}^{p} |\theta_{j_k}|^2 \right)$$

Simulation Study: Variable Selection

Data Generation: Survival Data

Competing Risks Survival Data

- Survival times generated from two exponential distributions using inverse transform sampling (one-year time period)

$$t_i = \frac{-\log(u_1)}{0.1 \cdot \exp(X\beta)}, i = 1, 2$$

- Cause-indicator **(1 - Cause of interest, 2 - Competing Risk)** generated from binomial experiment

$$\text{Binomial}[n, (1-p)^{\exp(X\beta_1)}]$$

where $p = 0.5$

- Uniform censoring: $U[0, M]$

- ~ **44 %** - Cause of interest, ~ **42 %** - Competing Risk, ~ **15 %** Censoring Rate

Data Generation: Covariate Generation

- True predictors generated from MVN with $\boldsymbol{\mu} = 0$ and pairwise correlations $\rho = 0.5$
- Noise predictors generated from MVN with $\boldsymbol{\mu} = 0$ and pairwise correlations $\rho = 0.1$
- We set $\beta_1 = (0, 1)^T$ and $\beta_2 = -\beta_1$
- N = 400
- Ratio of number of predictors (p)/ True predictors: 120/50, 1000/50

Data Generation: Simulation Settings

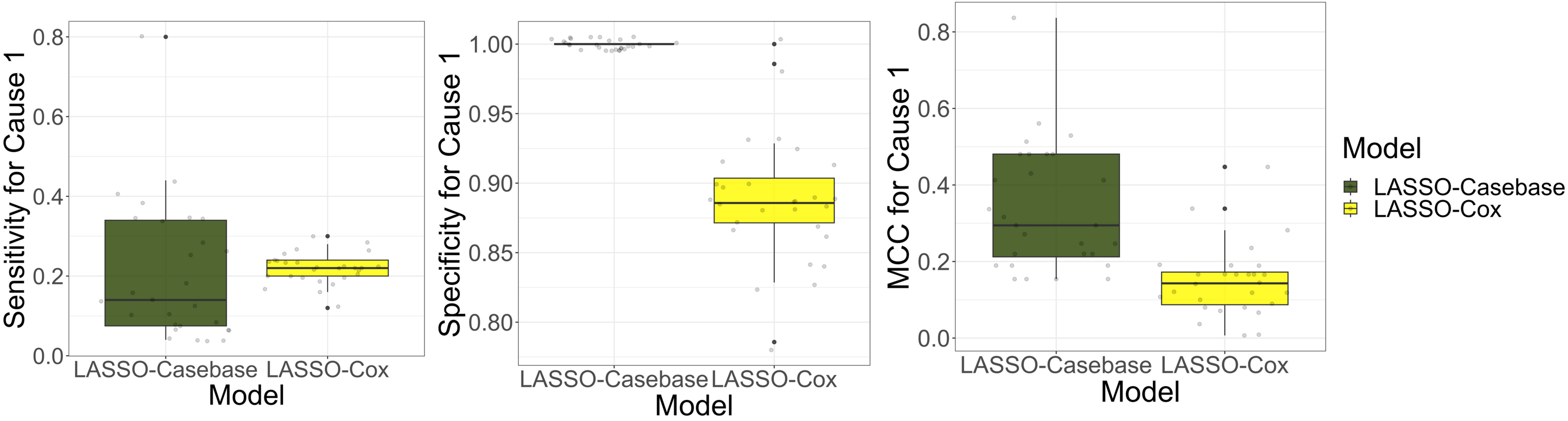
Compare Cause-Specific Hazard Models: Look at Cause 1

1. **Pen. Case-base with LASSO penalty (LASSO-Casebase)**

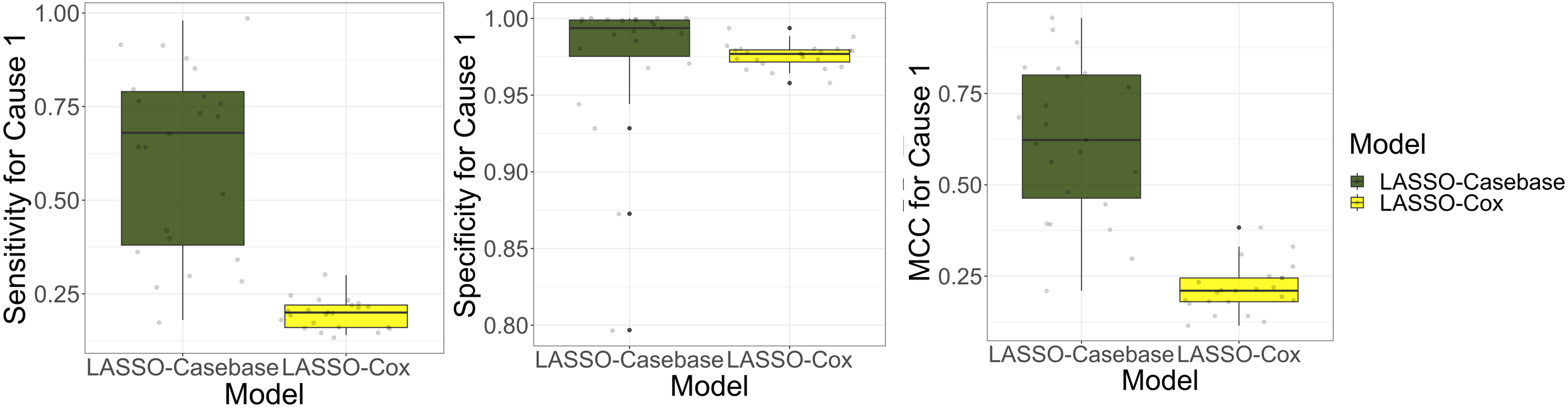
2. **Pen. cox with LASSO penalty (LASSO-Cox)**

- Tune Case-base using 5-fold cross-validation and Cox using 10-fold cross-validation, select lambda.min
- Time variable is transformed into log(Time) to model Weibull hazard in case-base and is not penalized
- **Comparison Metrics:** Sensitivity, Specificity, Matthew's Correlation Coefficient (MCC) (FP = FN = 0: +1, TP = TN = 0: -1)

Results: N = 400, p = 120, Tp = 50



Results: N = 400, p = 1000, Tp = 50



Simulation Study: CIF Prediction

Data Generation: Simulation Settings

Compare Cause-Specific and CIF Models:

- X generated from IID MVN

1. Pen. Case-base with LASSO penalty (LASSO-Casebase)
2. Pen. cox with LASSO penalty (LASSO-Cox)
3. Boosted Fine-Gray Model (FineBoost)

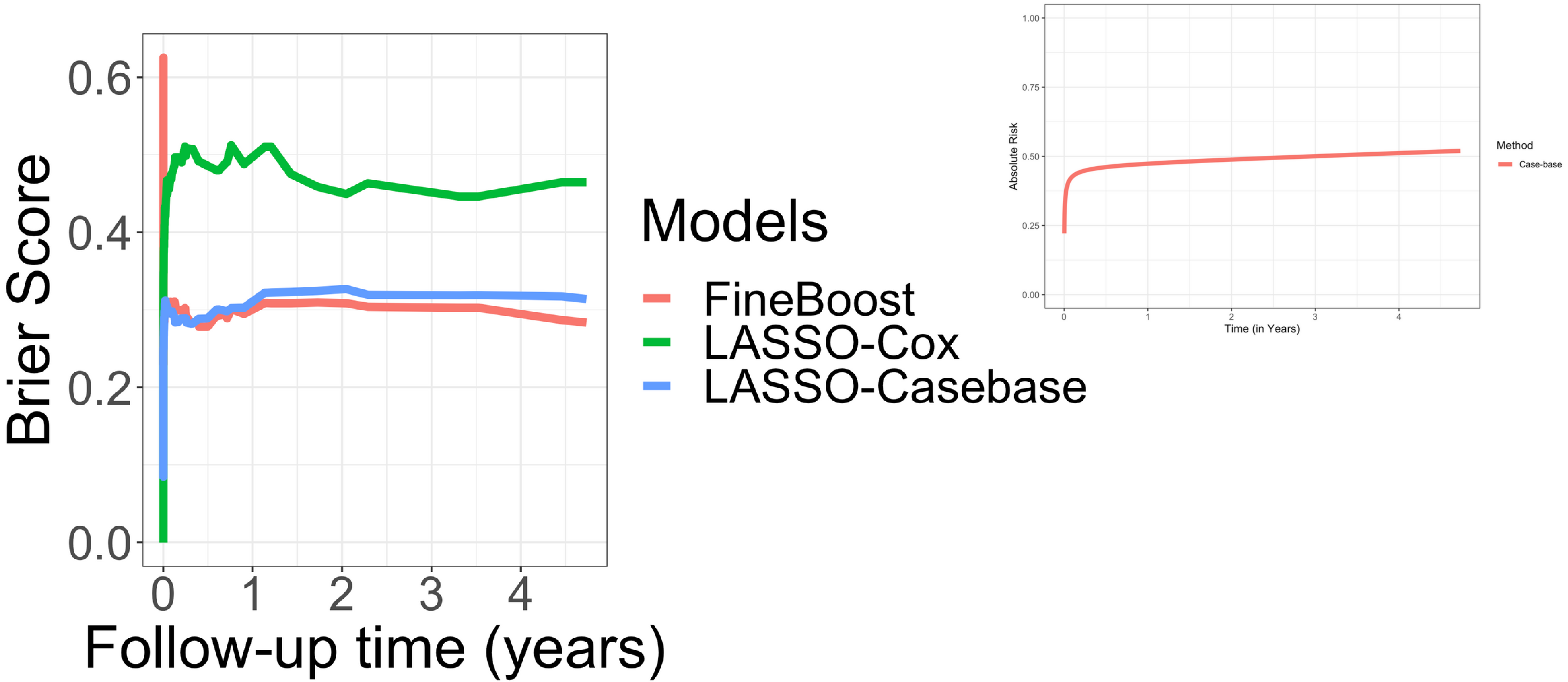
- **Comparison Metrics:** Time-dependent Brier Score

$$B(t) = \frac{1}{n}\sum_{i=1}^{n}\frac{\delta_i}{\widetilde{S}_i(t)}\sum_{j=1}^{m} I(Y_i(t)=j)\Big(I(Y_i(t)=j) - \widehat{P}(Y_i(t)=j)\Big)^2$$

δ_i : event indicator variable

$\widetilde{S}_i(t)$:Estimated censoring survival function for individual *i* at time t (KM)

Results: N = 400, p = 120, Tp = 50



Conclusions and Next Steps

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Cause-Specific Hazards Models

☑ Quantify Risk Factors: easy to interpret

☑ Treat competing risks as censored

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☑ Produce step-wise estimates of CIF (difficult to interpret)

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Conclusion

Cause-Specific Hazards Models

☑ Quantify Risk Factors: easy to interpret

☑ Performs comparably to cox in n > p and outperforms cox in p >n

CIF Models

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Next Steps

- Deal with uniform censoring randomness
- Bootstrapped confidence intervals for the Brier score (using .632+ rule)
- More CIF comparison models (Direct Binomial)
- **If time:** analysis on dataset (p > n) 2000 genes, 400 observations and time-event data on Bladder Cancer

Current Struggles:

- p > n cases running out of memory on Compute Canada :(